Original article

Anaphylaxis during anesthesia in France: An 8-year national survey

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Background: More attention should be paid to rare serious adverse events such as anaphylaxis to increase the safety of anesthesia.
Objective: To report the results of an 8-year survey of anaphylaxis during anesthesia in France.
Methods: Data from patients who experienced anaphylaxis between January 1, 1997, and December 31, 2004, were analyzed. Estimated incidences were obtained by combining this database with data from the French pharmacovigilance system by using a capture-recapture method. The number of patients exposed to the offending agents was obtained from data collected during the national survey of anesthesia practice.
Results: A total of 2516 patients was included. A diagnosis of IgE-mediated reaction was established in 1816 cases (72.18%). The most common causes were neuromuscular blocking agents ([NMBAs]; n = 1067; 58.08%), latex (n = 361; 19.65%), and antibiotics (n = 236; 12.85%). The median annual incidence per million procedures was higher for females 154.9 (5th-95th percentile, 117.2-193.1) than for males 55.4 (5th-95th percentile, 42.0-68.0). It reached 250.9 (5th-95th percentile, 189.8-312.9) for women in cases of allergic reactions to NMBAs. In children, a diagnosis of IgE-mediated reactions was obtained in 122 cases (45.9%). The most common causes were latex (n = 51; 41.8%), NMBAs (n = 39; 31.97%), and antibiotics (n = 11; 9.02%). In contrast with adults, no female predominance was observed.
Conclusion: The incidence of allergic reactions during anesthesia, estimated on a national basis, is higher than previously estimated. These results should be taken into account in the evaluation of the benefit-to-risk ratio of the various anesthetic techniques in individuals. The similar incidence of reactions according to sex before adolescence suggests a role for sex hormones in the increase of anaphylaxis observed in women. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: *Anaphylaxis, anesthesia, epidemiology, sex, children, neuromuscular blocking agents, latex, antibiotics*

The safety of anesthesia has been significantly improved during the last decades.[1] However, it may still be considered risky because it results from the exposure of a patient to a mixture of drugs that deliberately alter physiological functions in a short space of time. Complications frequently have multiple causes resulting from systems failure or from patients' underlying conditions.[2,3] To improve patient safety further, one should focus on education and guidelines, which should include the prevention, diagnosis, and treatment of rare but serious events that may occur during anesthesia. Adverse drug reactions have been recognized as one of the most common causes of death in medical practice.[4,5] Therefore, increasing attention has been paid over these last decades to allergic reactions that may occur during the very vulnerable perioperative period. However, despite systematic efforts aimed at characterizing the epidemiology of these reactions, it remains poorly defined. Indeed, the surveillance and analysis of adverse drug reactions represent a statistical challenge because these reactions are rare, random, and mostly independent from the successive exposure of patients to a low-risk intervention. Reporting processes range from spontaneous to statutory systems. However, because of possible biases and underreporting, these reporting systems are usually

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Abbreviations used
GERAP: Groupe d'Etudes des Réactions Anaphylactiques Peranesthésiques
HIS: Immediate hypersensitivity reaction
HSI-IgE: Immediate hypersensitivity reaction-IgE-mediated
HSI–non-IgE: Immediate hypersensitivity reaction not mediated by IgE
NMBA: Neuromuscular blocking agent

considered inappropriate for the assessment of adverse drug reaction rates or differences in incidence rates.[6-8] Nevertheless, when independent sources are available, the capture-recapture method, based on the intersection of the 2 data sources with the aim of identifying the number of common cases, can be used to estimate the number of unreported cases.[9-11]

In this report, data were collected by Groupe d'Etudes des Réactions Anaphylactiques Peranesthésiques (GERAP), a spontaneous reporting system that performs studies concerning hypersensitivity reactions occurring during anesthesia since 1985.[12-18] This was used to provide a complete description of the clinical symptoms, risk factors, and substances responsible for the reactions, with a special emphasis on the respective characteristics of reactions occurring in adults and children. The database was combined with data from the French drug surveillance system[19]—that is, the national official reporting system of adverse drug reactions—to estimate the real number of allergic reactions by using the capture-recapture method. Finally, the incidence rates of allergic reactions were estimated by using the number (denominator) and characteristics of the populations exposed to the various drugs responsible for the hypersensitivity reactions collected during the French survey of anesthesia, as conducted by the French Society of Anesthesia and Intensive Care.[20]

METHODS

Study design

Data from patients who experienced an immediate hypersensitivity reaction (HSI) during anesthesia suspected of being allergic in origin were prospectively included in the GERAP national register. The mechanism of the reaction (immediate hypersensitivity reaction-IgE-mediated [HSI-IgE] or nonimmunologic or immunologic other than immediate hypersensitivity reaction not mediated by IgE [HSI–non-IgE]) was assessed on the basis of a standardized diagnostic protocol performed in allergo-anesthesia outpatient clinics by members of the GERAP network.[21] The number of IgE-mediated reactions to hypnotics, opioids, neuromuscular blocking agents, and other agents was first described as a direct indication of the contribution of the various agents involved.

An additional analysis was then performed in an attempt to refine the incidence of anaphylaxis during anesthesia over the last 2-year period studied (2003-2004), using information provided by 2 additional databases. A specific analysis of hypersensitivity reactions during anesthesia, combining results from the GERAP database with results from the French Pharmacovigilance System database by using a capture-recapture method, was performed.[10,11] Estimates of the annual incidence of anesthesia and of the drugs used in the anesthetic protocols were obtained from the database of the French national survey of anesthesia conducted in 1996 by the French Society of Anesthesiology in close collaboration with Institut National de la Santé et de la Recherche Médicale.[20]

Data and assessments

GERAP. Cases recorded between January 1, 1997, and December 31, 2004, were included in the study. An intermediate analysis of part of the clinical cases reported here has been included in previous reports on a series of 3 consecutive 2-year surveys.[12,17,18] These previous cases are pooled with new results from our last 2-year survey (January 1, 2003, to December 31, 2004) to conduct a large database analysis. This allows us to compare results in children and adults for the first time.

Investigations were performed according to standardized procedures as recommended by the French Society of Anesthesiology and the French Society of Allergology.[21] The diagnostic protocol included a standardized questionnaire. Reactions were graded from I to IV depending on increasing severity (grade I, presence of cutaneous signs; grade II, presence of measurable but not life-threatening symptoms, including cutaneous effects, arterial hypotension, cough, or difficulty in mechanical ventilation; grade III, presence of life-threatening reactions: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm; grade IV, circulatory inefficacy, cardiac and/or respiratory arrest).

Data concerning allergy investigations were systematically recorded: type of skin tests performed (ie, skin prick test and/or intradermal test), dilution of the tested drug leading to a positive reaction, and cross-reactivity between neuromuscular blocking agents (NMBAs) in cases of adverse reaction to a NMBA.[22,23] Also recorded were the results of plasma histamine (RIA Histamine; Immunotech, Marseille, France) and serum tryptase monitoring (UniCAP Tryptase; Phadia SAS, Saint Quentin en Yvelines, France) during the adverse reaction, and of IgE-specific assays testing responses to quaternary ammonium (quaternary ammonium sepharose radioimmunoassay or P-aminophenylphosphoryl-choline radioimmunoassay),[24,25] latex, or antibiotics (Cap System; Phadia SAS) when available. Values above 9 nmol L^{-1} for histamine and 25 $\mu g\ L^{-1}$ for tryptase were considered positive.

Pathogenic mechanisms were defined in accordance with the nomenclature proposed by the European Academy of Allergy and Clinical Immunology and the World Allergy Organization.[26,27] IgE-mediated reactions (HSI-IgE) were diagnosed on the basis of skin test and/or IgE assay results consistent with the clinical history of the adverse reaction and the anesthetic protocol. Otherwise, the diagnosis of non-IgE–mediated reaction (HSI–non-IgE) was retained.

French Pharmacovigilance System. The French Pharmacovigilance System is the official national self-reporting system of adverse drug reactions based on a network of 31 regional centers that receive spontaneous adverse drug reaction reports from health professionals. After any declaration, a specific enquiry is conducted by a specialist, and a final diagnosis based on a causality assessment is established by applying the criteria of Moore et al,[28] which combine chronologic and semiologic criteria. A query in this database was performed on January 24, 2007, with the following terms: "anaphylactic reaction," "anaphylactoid reaction," and "anaphylactic shock." A total of 773 cases were identified in the period 2003 to 2004, and 159 cases related to anesthesia were considered eligible.

French national survey of anesthesia. The annual number of anesthesias performed in France in 1996, as well as the 95% CI, has been estimated in a national survey.[20] This study, initiated by the French Society of Anesthesia and Intensive Care, collected information that included the characteristics of patients (age, sex, American Society of Anesthesiologists status), the techniques of anesthesia, and the nature of the procedure for which anesthesia was required. All French private, public, and military hospitals were asked to participate in this survey. All anesthetic procedures were documented and collected over 3 consecutive days chosen at random during a 12-month period to obtain a representative sample of the annual activity. The participation rate of hospitals was 98%, and 62,415 questionnaires were collected, corresponding to 7,756,121 anesthetic procedures performed in France in 1996. For our incidence analysis, we had full access to data from this survey.

Causal drugs and incidence estimates. The number of IgE-mediated reactions to the responsible agents was initially established by using the GERAP database. These results were merged with data from our 2 additional databases. To assess the incidence of anaphylactic reactions during anesthesia, we estimated (1) the annual number of anaphylactic reactions related to anesthesia, and (2) the annual number of anesthetics performed in France within the 2003 to 2004 period.

Estimation 1: Annual number of anaphylactic reactions related to anesthesia. The annual number of anaphylactic

reactions related to anesthesia was obtained by a capture-recapture method[10,11] using the 2 independent sources described: the GERAP network database and the French Pharmacovigilance System database. We adopted the following inclusion criteria for both sources: IgE-mediated reaction related to anesthesia, reaction occurring in the years 2003 to 2004, and reaction occurring in a geographic area covered by both sources (63% of French population). Patients with identical geographic location, sex, and age (±3 years) were considered potential overlaps. Each of these cases was manually checked to identify overlapping patients. After identifying the overlaps, log-linear models for the capture-recapture method were used to estimate the total number of anaphylaxis episodes in the study area, as well as the 95% CI. An extrapolation including a sex and age standardization provided the total number of annual episodes of anaphylaxis in France.

Estimation 2: Annual number of anesthesias performed in France. The annual number of anesthesias performed in France in 1996 and the 95% CI have been estimated previously in a national survey.[20] For our incidence analysis, we had full access to data from this survey. As a result of extrapolating the evolution of annual procedures provided by medico-administrative data, and the stability of the number of vials of neuromuscular blocking agents used in France—5,879,000 from 1997 to 1998, 6,157,000 from 1999 to 2000, 5,721,000 from 2001 to 2002, and 6,081,000 from 2003 to 2004[29]—we consider that the number of anesthetic procedure remained stable in France during the period 1996 to 2004.

Estimation of the incidence of anaphylaxis during anesthesia. The incidence of anaphylaxis during anesthesia was estimated by combining estimations (1) and (2) in the following formula:

Incidence = annual number of anaphylactic reactions related to anesthesia/ annual number of anesthesias performed in France.

Incidences were calculated for all patients according to sex, age class (/5 years), and the more frequently involved causal drug present in both sources (opioids, neuromuscular blocking agents, hypnotics). Allergic reactions to latex are not reported to the national pharmacovigilance system, and information concerning the use of antibiotics during anesthesia was not recorded in the survey of anesthesiology practice in France. Therefore, the methods providing estimates of incidences of allergic reactions to latex and antibiotics could not be used. With this limitation in mind, incidences were estimated by taking into account the proportion of allergic reactions identified by the GERAP network. It was assumed that all patients had potentially been exposed to latex and that the incidence for antibiotics was derived from the estimated incidence of allergic reactions and the relative contribution of antibiotics in the GERAP database.

The 95% CIs of estimated incidences were evaluated by the Monte Carlo simulation technique.[30] This method consists of randomly generating a high number (ie, 10,000) of ratios (the number of cases/the number of exposures) and calculating the median and 5th to 95th percentile intervals of the distribution of obtained ratios. The numerators and the denominators of ratios were generated from Poisson distributions with the observed number of cases and the number of exposed persons, respectively, as mean values.

Statistical analysis was performed by using the SAS 8.02 software (SAS Institute Inc, Cary, NC). Values were expressed as mean ± SD or percentages. Intergroup comparisons used *ad hoc* methods (Pearson χ^2 test, Mann-Whitney test, ANOVA, or correlation). A P value ≤.05 was considered statistically significant.

RESULTS

GERAP database

A total of 2516 patients were included. At the end of the allergy workup, a diagnosis of IgE-mediated immediate hypersensitivity reaction was established in 1816 cases (72.18%), whereas the remaining 700 cases (27.82%) were considered non–IgE-mediated hypersensitivity reactions. The rate of hypersensitivity reactions and the distribution according to the mechanism of hypersensitivity remained stable throughout the entire study period.

TABLE I. Agents involved in IgE-mediated reactions during anesthesia (1816 patients, 1851 substances) between January 1, 1997, and December 31, 2004

Causal agent	Reactions (%)	No. of patients
NMBAs	58.08	1067
Succinylcholine	33.40	356
Rocuronium	29.30	313
Atracurium	19.30	206
Vecuronium	10.20	109
Pancuronium	3.60	38
Mivacurium	2.50	27
Cisatracurium	1.70	18
Total	100	
Latex	19.65	361
Antibiotics	12.85	236
Penicillin	49	115
Cephalosporin	37	88
Others	14	33
Total	100	
Hypnotics	2.34	43
Propofol	55.80	24
Midazolam	32.60	14
Pentothal	9.30	4
Ketamine	2.30	1
Total	100	
Opioids	1.69	31
Morphine	35.5	11
Fentanyl	22.6	7
Sufentanil	22.6	7
Nalbuphine	12.9	4
Remifentanil	6.5	2
Total	100	
Colloids	3.43	63
Gelatin	88.9	56
Hetastarch	9.5	6
Albumin	1.6	1
Total	100	
Local anesthetics	0.33	6
Bupivacaine	50.0	3
Lidocaine	33.3	2
Mepivacaine	16.7	1
Total	100	
Other agents	2.40	44
Patent blue	25.0	11
Methylene blue	2.3	1
Propacetamol	20.5	9
Aprotinin	11.4	5
Protamine	9.1	4
Nonsteroidal anti-inflammatory drugs	6.8	3
Papain	6.8	3
Nefopam	4.5	2
Ethylene oxide	2.3	1
Steroids	2.3	1
Hyaluronidase	2.3	1
Metabisulfite	2.3	1
Povidone	2.3	1
Contrast media	2.3	1
Total	100	

The most common causes of anaphylactic reactions were NMBAs (n = 1067; 58.08%), followed by latex (n = 361; 19.65%) and antibiotics (n = 236; 12.85%; Table I). Succinylcholine (n = 356; 33.4%) was most frequently incriminated, followed by rocuronium (n = 313; 29.3%), atracurium (n = 206; 19.3%), and vecuronium

TABLE II. Estimated annual incidence of IgE-mediated allergic reactions during anesthesia

Causal agent	Estimated annual no. of cases	Estimated annual incidence (/million) Median (5th-95th percentile)		
		Male	Overall	Female
Overall	780 (555-1005)	55.4 (42.0-69.0)	100.6 (76.2-125.3)	154.9 (117.2-193.1)
Neuromuscular blocking agents	458 (326-590)	105.5 (79.7-132.0)	184.0 (139.3-229.7)	250.9 (189.8-312.9)
Latex	155 (110-200)*	32.6 (24.7-40.5)	59.1 (44.8-73.6)†	91.0 (68.9-113.4)
Antibiotics‡	101 (72-131)	—	—	—
Other agents‡	80 (57-103)	—	—	—

*Extrapolation based on cases identified in the GERAP database.
†All patients were considered to be exposed to latex during the perioperative procedure.
‡Number of patients exposed not recorded in the survey of anesthesia practice.

(n = 109; 10.2%), whereas reactions to other nondepolarizing NMBAs were less common. Reactions involving latex initially increased to reach a plateau from 2000 to 2004. Reactions involving antibiotics, after a rapid increase, remained stable from 1998 to 2004. Hypnotics, opioids, and local anesthetics were rarely involved. Colloids were incriminated in 63 cases, and other substances in 44 cases, with an unexpectedly high number of reactions involving dyes from 2002 to 2004.

Estimation of the incidence of allergic reactions during anesthesia

During the period from 2003 to 2004, the pharmacovigilance network registered 159 eligible cases and the GERAP network 281. Among the 91 potential overlap cases, 30 were identified as real overlaps. From this data, the calculation provided an annual number of 625 (5th-95th percentile, 445-805) cases in France. This annual number can be extrapolated to 780 (5th-95th percentile, 555-1005) when cases involving latex, which are recorded only in the GERAP database, are included (Table II). The completeness of registration was 17.1% for pharmacovigilance and 22.2% for the GERAP network. Given the 7,756,121 (5th-95th percentile, 7,374,848-8,137,394) anesthetic procedures performed annually in France and the 780 (5th-95th percentile, 555-1005) IgE-mediated reactions related to these procedure, the estimated median annual incidence was 100.6 (5th-95th percentile, 76.2-125.3) per million procedures. This incidence was higher for females (5th-95th percentile, 154.9 [117.2-193.1]) than males (5th-95th percentile, 55.4 [42.0-68.0]). It reached a maximum of 250.9 (5th-95th percentile, 189.8-312.9) for women and 105.5 (5th-95th percentile, 79.7-132.0) for men when allergic reactions to NMBAs had occurred. Estimations of the incidence according to sex and age class (/5 years) are presented in Fig 1.

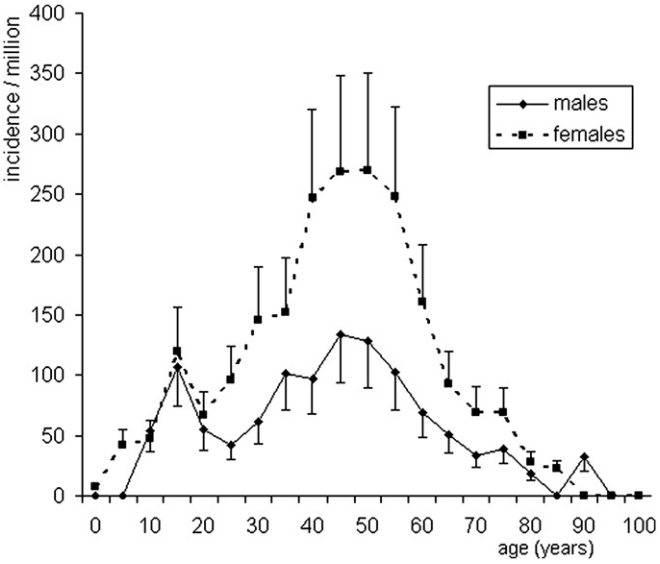

FIG 1. Estimated incidence of IgE-mediated allergic reactions according to sex and age ranges (5 years).

Associated factors

Results regarding associated factors are described according to information collected in the GERAP database. A history of previous anesthesia was not a risk factor for immediate hypersensitivity reaction except in patients with a history of adverse reaction during a previous anesthesia. No difference was observed between IgE and non–IgE-mediated reactions when the incidences of atopy (16.32% vs 17.47%; P = nonsignificant), asthma (9.90% vs 8.30%; P = nonsignificant), or drug intolerance were compared (18.54% vs 16.10%; P = nonsignificant). A history of food intolerance was more frequently reported in case of IgE-mediated reactions (8.49 vs 3.64; $P < .0001$; Table III). This difference was related to a higher proportion of atopic patients who were sensitized to latex. Allergy to latex was significantly associated with a history of atopy, asthma, or food intolerance ($P < .0001$). Moreover, in 176 of 361 patients (48.6%) who experienced an IgE-mediated reaction to latex, careful retrospective assessment of their medical history revealed the presence of symptoms suggestive of latex sensitization such as fruit allergy or intolerance to materials containing rubber latex before the reaction. Allergy to antibiotics was associated with a positive history of drug intolerance ($P < .01$), whereas no significant risk factors could be identified regarding allergy to NMBAs. Anaphylaxis to an NMBA was observed in 131 patients (12.6%) who had no history of anesthesia before the current adverse reaction, and therefore no previous exposure to any NMBA.

Clinical features

Clinical features are described according to information collected in the GERAP database. IgE-mediated and non–IgE-mediated immediate hypersensitivity reactions cannot be distinguished on the basis of clinical symptoms alone. However, clinical manifestations were more severe in patients with documented IgE-mediated than in patients presenting with a non–IgE-mediated reaction ($P < .0001$; Fig 2, *A*). Most IgE-mediated reactions were grade 3 (n = 1092; 60.132%), whereas non–IgE-mediated reactions were mainly grade 1 (n = 372; 53.143%).

TABLE III. Clinical symptoms, tryptase levels, and history of allergies according to mechanism of immediate hypersensitivity reactions during anesthesia in the general population between January 1, 1987, and December 31, 2004 in France

Clinical symptoms	HSI-IgE (%)	HSI–non-IgE (%)
Cutaneous symptoms	70.24	95.34
Erythema	47.27	68.41
Urticaria	20.31	25.62
Angioedema	11.08	8.30
Cardiovascular symptoms	84.04	36.39
Hypotension	21.861	20.14
Cardiovascular collapse	54.901	10.57
Cardiac arrest	5.34 (n = 97)	0.29 (n = 2)
Bronchospasm	41.35	19.29
Median tryptase μg L^{-1}	45	6
Median (range)	(1-1020)	(1-106)
Atopy	16.32	17.47
Asthma	9.90	8.0
Drug intolerance	18.54	16.10
Food intolerance	8.49	3.64

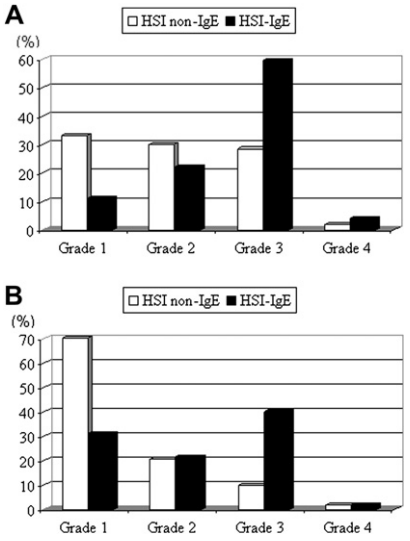

FIG 2. Frequencies of clinical severity grade of IgE-mediated and non–IgE-mediated hypersensitivity reactions between January 1, 1997, and December 31, 2004, in France in the general population **(A)** and in children **(B)**.

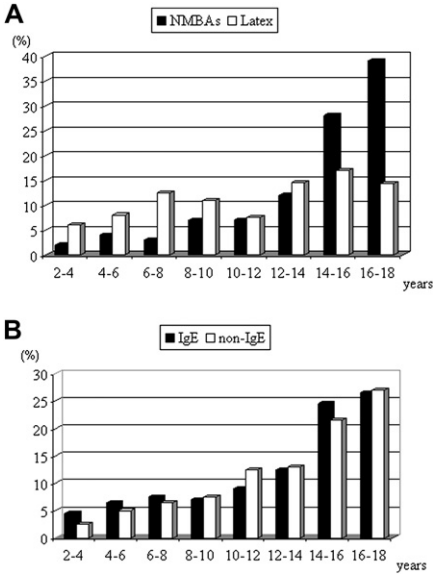

FIG 3. Distribution of IgE-mediated and non–IgE-mediated hypersensitivity reactions in children according to age ranges (years) between January 1, 1997, and December 31, 2004, in France for latex and NMBAs **(A)** and for IgE and non–IgE-mediated reactions **(B)**.

The various clinical features observed during IgE-mediated and non–IgE-mediated immediate hypersensitivity reactions are summarized in Table III. Cutaneous symptoms were absent in one third of IgE-mediated reactions (non–IgE-mediated 95.34% vs 70.24% IgE-mediated reactions; $P < .0001$), whereas angioedema was more frequently observed in IgE-mediated reactions. Cardiovascular symptoms (84.04% vs 36.39%; $P < .0001$) were more frequent in cases of IgE-mediated reactions, with a higher frequency of cardiovascular collapse (non–IgE-mediated 10.571% vs 54.901% IgE-mediated reactions; $P < .0001$). Cardiac arrest was noticed in 97 cases of IgE-mediated reactions. Bronchospasm, another symptom classically associated with a higher reaction severity (grade 3 or 4), was also more frequent in the case of IgE-mediated reactions (non–IgE-mediated 19.286% vs 41.355% IgE-mediated reactions; $P < .0001$).

Clinical symptoms may also occur as an isolated phenomenon. In HIS-IgE reactions, cardiovascular collapse was the sole feature in 164 cases, hypotension in 32 cases, cardiac arrest in 45 cases, bronchospasm in 26 cases, and cutaneous symptoms in 53 cases. Angioedema never occurred alone. Cutaneous symptoms were the sole feature in 375 non–IgE-mediated reactions.

Tryptase levels were significantly elevated (>25 μg L^{-1}) in 68% of IgE-mediated reactions (median, 45 μg L^{-1}; range, 1-1020), whereas an increased level was observed in 4% of non–IgE-mediated reactions (median, 6 μg L^{-1}; range, 1-106; Table III).

Features particular to children

A subgroup analysis was conducted in children under the age of 18 years. A total of 266 children were included. A diagnosis of IgE-mediated reaction was made in 122 cases (45.9%). The distribution according to age and mechanism of the reaction is displayed in Fig 3, *A*.

The various incriminated substances differ significantly from those for adult patients. Latex was the most frequently incriminated substance (n = 51 cases; 41.8%), followed by NMBAs (n = 39; 31.97%) and antibiotics (n = 11 cases; 9.02%). The distribution of sensitization according to age was significantly different for these substances. Sensitization to latex was diagnosed as of 2 years of age, and its distribution was quite homogenous in children, whereas the number sensitized to NMBAs or antibiotics became more frequent in adolescents (Fig 3, *B*).

In contrast with the results observed in adults, no significant differences were observed in regard to the sex distribution in children for both mechanisms (IgE-mediated reactions: male, n = 61 cases [50%], female, n = 61 cases [50%]; non–IgE-mediated reactions: male, n = 78 cases [55.2%], female, n = 66 cases [45.8%]).

As reported in adults, no differences were observed between IgE-mediated and non–IgE-mediated reactions when the incidences of atopy (31.15% vs 23.60%; P = nonsignificant), asthma (14.75% vs 11.81%; P = nonsignificant), or drug intolerance

TABLE IV. Clinical symptoms and history of allergies according to mechanism of immediate hypersensitivity reactions during anesthesia in children between January 1, 1997, and December 31, 2004 in France

	HIS-IgE (%)	HSI–non-IgE (%)
Cutaneous symptoms	83.6	97.9
Cardiovascular symptoms	42.62	20.83
Bronchospasm	42.62	15.28
Atopy	31.15	23.6
Asthma	14.75	11.81
Drug intolerance	15.58	20.14
Food intolerance	13.93	4.17

were compared (15.58% vs 20.14%; P = nonsignificant). However, once again, a history of food intolerance was more frequently reported in the case of IgE-mediated reactions (13.93 vs 4.17; $P < .01$; Table IV). This difference was related to a higher proportion of atopic patients who were sensitized to latex. In addition, atopy (31.15% vs 16.32%; $P < .0003$) and a history of food intolerance (13.93% vs 8.49%; $P < .004$) were more frequent in children with an IgE-mediated hypersensitivity reaction compared with adults.

Clinical manifestations were more severe in IgE-mediated than in non–IgE-mediated reactions ($P < .0001$). Most IgE-mediated reactions were grade 3 (n = 50; 40.98%), whereas non–IgE-mediated reactions were mainly grade 1 (n = 100; 69.44%).

The various clinical features observed during IgE-mediated and non–IgE-mediated immediate hypersensitivity reactions are summarized in Table IV. Cardiovascular symptoms were more frequent in cases of IgE-mediated reactions than in non–IgE-mediated reactions ($P < .0002$), but this difference was less pronounced than in adults. Only 1 episode of circulatory collapse was reported, and it occurred in a 5-year-old girl sensitized to atracurium. Bronchospasm was also more frequent in case of IgE-mediated reactions ($P < .0001$).

DISCUSSION

This combined analysis of 3 different databases allows us to provide a nationally based estimate of the incidence of immediate IgE-mediated allergic reactions occurring during anesthesia, according to sex, age, and causal substance. To our knowledge, this report represents the first attempt to provide an accurate estimate of the frequency of allergic reactions using the capture-recapture method and the largest cohort of patients available in the literature. It confirms the general view that immediate-type hypersensitivity reactions are largely underreported, with a higher incidence (100.6 [76.2-125.3] per million procedures) of allergic reactions than previously reported,[14,31] with women at significantly higher risk than men. In addition, this study highlights for the first time the specificities of allergic reactions in children. The similar incidence of allergic and nonallergic reactions according to sex before adolescence strongly suggests a role for sex hormones in the increase of immediate hypersensitivity reactions observed in women. These results should be taken into account when evaluating the benefit-to-risk ratio of the different anesthesia techniques in the different subsets of the population.

The leading causes of allergic reactions in France are NMBAs, followed by latex and antibiotics used for antimicrobial prophylaxis. These results call for an active policy of risk reduction, combining a reduction of unnecessary exposure to potentially sensitizing compounds and a systematic search for possible risk factors before anesthesia. The wide diversity of causal agents involved in allergic reactions also underlines the necessity to refer these patients to centers with experience in drug allergy investigation to identify the responsible agent and provide recommendations for future anesthetic procedures.

The need for research in drug allergy has been strongly advocated.[32] However, the surveillance and analysis of adverse drug reactions represent a statistical challenge because these reactions are rare, random, and mostly independent from the successive exposure of patients to a low-risk intervention.[7] Because of possible biases and underreporting, spontaneous reporting systems are usually considered inappropriate for the assessment of adverse drug reaction rates.[6,8,33] The capture-recapture method has been used by epidemiologists to estimate the prevalence or incidence of diseases in human beings.[10,11,34] It represents a helpful tool for estimating frequency when several sources of information are available and can be matched. Cases identified by each source should be real cases and true matches, identified in the same population, in the same geographic area, during the same period. These conditions have been fulfilled in the current study. Another important condition is to be able to provide a precise estimate of the number of patients exposed to the potentially offending agent. This was achieved by accessing the database concerning anesthesia in France in 1996,[20] considering that the number of anesthesias performed in France within the study period has remained stable. This assumption can be regarded as acceptable because the market shares of the various drugs used in anesthesia in France within this period remained relatively stable.

In our series, a significant female predominance was observed only in adults. This increased incidence of reaction remained significant even when the frequency of reaction was adjusted for the number of procedures performed. In addition, IgE-mediated reactions to latex were observed at a younger age in children compared with IgE-mediated reactions to NMBAs. Such sex differences and changes in the sex ratio after puberty have been previously reported in the literature for allergic reactions to proteins in the case of asthma, atopic eczema, and food allergy.[35] The hypothesis of a possible cross-sensitization with quaternary ammonium ion–containing compounds such as cosmetics has long been proposed to explain the increased incidence of immediate hypersensitivity reactions observed in women.[36] However, this hypothesis remains to be confirmed, and in their comprehensive study on the possible implication of household chemicals in sensitization to NMBAs, Florvaag et al[37] failed to identify a possible responsible agent. Our results demonstrate that the suspected influence of sex hormones on immediate-type IgE-mediated reactions is not limited to sensitization to proteins but also involves allergy to low-molecular-weight compounds. Although the mechanism of sensitization to small molecules might differ in some cases from those to proteins,[38] the rate of sensitization to these drugs appears to be also influenced by sex hormones. Indeed, estrogens have been showed to act as immunomodulators[39] able to skew the immune response toward a T_H2 profile by acting on dendritic as well as T cells and to enhance mast cell activation.[39-41] Similarly, progesterone has been showed to potentiate IgE formation in mice sensitized to house dust mite.[42] In addition, the higher incidence of non–immune-mediated hypersensitivity reactions observed in our female patients suggests that estrogens might also play a role in this increased rate of nonspecific effector

cell activation and potentially in the enhanced synthesis and release of allergic mediators.[43]

A high incidence of allergic reactions to NMBAs is reported in our study. Of all the drugs studied that elicit immediate allergic reactions, these compounds demonstrate a number of intriguing departures from the usually accepted explanations of the mechanisms underlying the allergic immune response to "small" molecules.

It has been generally assumed that conjugation of low-molecular-weight compounds to a carrier protein was necessary for cross-linking of mast cell–bound IgE and the subsequent release of mediators of allergy. In 1983, Baldo and Fisher[44] established that the quaternary ammonium ions and the tertiary amines present in NMBAs were part of the epitopes involved in allergic reactions to these drugs. Because the substituted ammonium ions of NMBAs are responsible for both the neuromuscular blocking and allergenic properties and because there are at least 2 of these groups separated by a distance of 1 to 1.45 nm, it was suggested that NMBAs elicit allergic mediator release by binding to and bridging combining sites of adjacent cell-bound complementary IgE molecules via the ammonium groups. The divalency of NMBAs explains the allergen-induced mediator release in a sensitized subject even in the absence of protein binding.

Another intriguing feature relates to the immunologic dogma of previous exposure. In our series, as in previous reports,[12,18,45,46] a large proportion of subjects reacted on their first exposure to an NMBA. Because the NMBAs' epitopes involved in allergic reactions occur widely, not only in many drugs but also in foods, cosmetics, disinfectants, and industrial materials, there has been speculation that the origin of allergic sensitization could be environmental agents or drugs containing an ammonium ion or a tertiary amine. Thus, allergenic cross-reactivity has been proposed to explain the lack of previous exposure seen in many of the patients with allergy. However, the theory of environmental sensitization is not confirmed. Recently, Florvaag et al,[47] taking advantage of the large difference in the incidence of allergic reactions to NMBAs, which is more than 6 times greater in Norway than Sweden, investigated the possible sensitizing role of several environmental factors. They failed to demonstrate any differences regarding the use of household chemicals or other environmental factors. However, they reported the presence of IgE antibodies to pholcodine, a morphinelike alkaloid with a quaternary ammonium ion, used in cough suppressants without restriction in Norway but not in Sweden, in 6% of blood donors from Norway but in none of the Swedish donors. In an international prevalence study, these authors provided additional support to the hypothesis of the possible sensitizing role of pholcodine.[48] However, the results suggest that other, yet unidentified substances may lead to IgE-sensitization toward NMBAs.

The study of possible risk factors for anaphylactic reactions appears somewhat disappointing, because the relatively low incidence and prevalence of anesthetic systemic reactions in the general population will limit the ability to identify patients at risk. Indeed, the majority of patients with a history of atopy, asthma, family history, female sex, previous exposure, allergy to cosmetics, and nonanesthetic drugs will undergo uneventful anesthesia. On the contrary, a previous anesthetic hypersensitivity reaction or a history of an unexplained or undocumented anesthetic event are significant risk factors and make investigation mandatory.

When an allergy to latex was found in our series, a large proportion of reactors had a previous history of symptoms, indicating a possible sensitization to latex. This demonstrates that a standard preanesthetic questionnaire is not sufficiently reliable to detect latex allergy because patients will not always report signs indicating a possible sensitization when asked about allergies. A specific inquiry about fruit or latex allergy should be part of the routine preoperative interrogation. In addition, a number of factors have been identified as predisposing to anaphylaxis after exposure to latex. Children with spina bifida or those who have undergone multiple operations are a major at-risk group for latex. This is confirmed by our results indicating a large proportion of reactions involving latex in children. In addition to detecting patients at risk, anaphylactic reactions to latex potentially could be reduced by avoiding latex exposure in patients with spina bifida from birth and avoiding exposure to latex in operating rooms by provision of a latex-free environment in children's hospitals.[49,50]

This strategy of prevention by limiting patient exposure to drugs considered high risk has also been shown to be effective in the case of succinylcholine by limiting its use to patients requiring emergency intubation and not using it as a prelude to a long-acting NMBAs.[51] These results and the high incidence of allergic reactions to NMBAs observed in women are a strong incentive for a policy of risk reduction through avoidance of unnecessary exposure to potentially sensitizing compounds. Our results should be considered when evaluating the relative risk of regional versus general anesthesia in women as well as in children. This consideration can be extended to the indications for antimicrobial prophylaxis, the use of which should be supported by an appropriate benefit-to-risk ratio estimate, as recently highlighted in the revised recommendation for prevention of infective endocarditis.[52]

Finally, considering the large number of drugs, diagnostic reagents, devices containing latex or other sensitizing compounds, antiseptics, and blood products that are routinely used in anesthesia, all of which may be involved in a reaction, a systematic investigation of suspected hypersensitivity reactions is mandatory. In view of the relative complexity of allergy investigation, an active policy should be promoted to identify patients at risk, provide any necessary support such as expert advice to anesthetists, and refer patients to centers with experience in drug allergy investigation.

Clinical implications: The incidence of allergic reactions during anesthesia is higher than previously estimated. A role for sex hormones in the increase of anaphylaxis observed in women is suggested.

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